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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,832	CHOW ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 15-17, 20-, 24-25, 28-31, 33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 15-17, 20-, 24-25, 28-31, 33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment filed October 31, 2007 has been received and entered. Claims 2-14, 18-19, 21-23, 26-27, 32 have been cancelled, while claim 1 has been amended.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claims 1, 15-17, 20, 24-25, 27-31 and 33-34 are under consideration.

Withdrawn-Claim Rejections- New Matter

Claims 1, 15-18, 20, 24-25 and 27-34 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claims.

Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15-17, 20, 24-25, 27-31 and 33-34 are rejected under 35 U.S.C. 112, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Nature of the Invention:

The claims are directed to methods for treating HIV infection in a human caused by HIV, wherein HIV entry into immune cell is facilitated by a CCR5 receptor by transplanting a stem cell rich population of cells (cord blood cells) obtained from a human donor having beneficial gene that is a homozygous polymorphism in a CCR5 gene thereby treating said HIV infection. In further

embodiments, polymorphism is either a 32-basepair deletions in coding region or CCR5m303 or in promoter region, additionally comprising identification of the HLA genotype or phenotype of cells, screening cell sample from human donor to identify the stem cell rich population of the cell that has polymorphism in CCR5 gene by different techniques. Claims 28-31 further comprise identification of HLA genotype via high throughput such that genotype or phenotype of such cell is compatible with HLA genotype or phenotype of human. Newly added claims embrace transplantation of multiple samples of stem cell rich population and wherein multiple samples of cells with the beneficial gene have an HLA unmatched genotype or phenotype.

Breadth of the claims:

The claims are broadly directed to treating HIV infection in humans infected with HIV, at any stage of the disease by transplanting via any route a population of cord blood cells having a beneficial gene that is homozygous polymorphism in any part of the CCR5 gene subsequently limiting to either promoter or coding region of CCR5. It is noted that breadth of instant claims do not limit the treatment of HIV infection at any specific stage, thus embrace early as well as late stage of viral infection in human patients. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of these, aspect must be shown to a reasonable extent so that one of the ordinary skills in the art would be able to practice the invention without any undue burden being on such Artisan.

Guidance of the Specification and The Existence of Working Examples:

The specification provides a general description of polymorphisms of genes encoding ligand for the co receptor CCR5 and CXCR4 that confer resistance to HIV (page 1). The specification also states that HLA alleles influence HIV-1 disease progression (see pages 1-2). Remaining specification discloses definition of terms, general description of biological method, method of stem cell transplant and HLA

genotyping. It is noted that application as filed itself states "the discovery of the fact that certain polymorphism confer resistance to HIV has led to proposal of therapies which repopulate the immune system with cells that could confer resistance to HIV infection". The specification also states, "nature of such therapies should reduce side effect" suggesting that treatment or prevention against HIV infection by transplanting stem or any other cell to confer resistance to HIV infection was just a theory that was not reduced to practice at the time of filing of this application as neither art nor specification specifically teaches how stem cell having beneficial gene that is polymorphism in a CCR5 gene would have prevented or treated HIV infection.

Applicant example only provides a schematic of proposed therapy in human without disclosing any specific (see example 1). It is noted that example 2 describes screening of target containing a nucleic acid sequence corresponding to that of the CCR5 delta 32 polymorphism and prophetically contemplates intravenous transfusion of samples with the polymorphism and the closest HLA match into patients

State of the Art and Predictability of the Art:

The state of the art recognizes that CCR5 has a primary role in HIV transmission. In particular, it has been found that a 32 base pair deletion in CCR5 confers resistance to HIV infection (Lehner et al Trends in Immun., 2002, 23(7): 347-351, page 348, col. 1, para. 1). The art teaches that the *CCR5*Δ32 is a naturally occurring knockout deletion variant that leads to effectively restrict HIV-1 cell entry in homozygous people (see Kaur et al Human Immunology 68, 454–461, 2007 and references therein), but others have suggested that this protection was incomplete as numerous studies reported seropositive individuals that were homozygous for Δ32, demonstrating that protection is incomplete (see page 390, col. 2, para.1, Arenzana-Seisdedos et al Semin Immunol. 2006;18(6):387-403 and references therein). This suggests that CCR5 expression is altered in these individuals, and

that this alteration affects the HIV-1 replication *in vivo*. Recently, it has been reported that because distributions of *CCR5* polymorphisms vary greatly among different populations, it is hypothesized that these polymorphisms influence HIV-1 transmission and disease progression differentially according to their distribution in a race-specific manner. For instance, Kaur et al (Human Immunology 68, 454-461, 2007 and references therein) disclose percent allele frequencies corresponding to five SNPs in the promoter region of CCR5 at positions 59029, 59353, 59356, 59402, and 59653 in the HIV- 1 infected individuals. It is noted that frequency of allele CCR5*59402A was increased in the HIV-positive cohort compared with healthy control (see table 3) indicating that *CCR5*59402A allele might favor the likelihood of acquisition of HIV-1 infection and development of AIDS (see Kaur et al page 459, col. 1, para. 1). In the instant case, the specification fails to provide any nexus between transplanting cord blood cells having homozygous polymorphism in any region of CCR5 gene in an individual to the treatment against HIV infection of any stage in an individual of any race as embraced by the breadth of the claims.

The state of art also teaches that 32 base pair deletion in CCR5 confers resistance to HIV infection, but numerous studies reported co receptor usage in HIV infection. For instance, Naif et al (Journal of Virology, 2002, 72(1): 3114-3124, art of record) show that a primary HIV isolate from an HIV-infected CCR5-deficient person can infect both macrophages and T-cell lines via the co receptor CXCR4. This is further supported by the studies of Gorry et al showing HIV-1 tropism for macrophages and microglia can be restricted at the entry level by a mechanism independent of co receptor specificity (Gorry et al Journal of Virology 2001; 75(21): 10073-89, art of record). It is noted that Gorry et al use CCR5 and CXCR4 inhibitorsTAK-779 and AMD3100 to show that two highly macrophage tropic isolates (that usually require CCR5 for entry into immune cell) entered microglia primarily via CXCR4. This clearly supports the fact that HIV-1 tropism for macrophage and microglia is independent of any specific receptor. Gorry et al state

"M-tropic HIV-1 viruses typically utilize CCR5 for entry in primary $CD4^+$ cells (emphasis added), however, our studies showed that CCR5 usage is neither necessary nor sufficient for HIV. We found that 6 of 11 primary R5 isolates could not replicate in monocyte-derived macrophages (MDM) and microglia. These findings are consistent with previous studies that failed to establish a strict correlation between CCR5 usage and macrophage-tropism and showed a lack of M-tropism by some R5 HIV-1 clones obtained from brain, lymph node, spleen, and lung tissue". Furthermore, Sheppard et al (Journal of acquired Immune Deficiency Syndrome, 29: 307-313, art of record) disclose that delta 32 mediated resistances to HIV are incomplete and are associated with acquisition of exclusively-X4 variants of HIV-1 (abstract, pp311). In addition, it is emphasized that Sheppard et al state "further studies are needed to explore the relationship between pattern of co receptor usage and mechanism of pathogenesis (pp312, column 2, paragraph 2). The cited art clearly teaches HIV-1 entry into immune cells use other receptor in conjunction with CCR5 and claimed method does not preclude the entry of HIV by other receptor. An artisan would have to perform undue experimentation to adminster appropriate number of stem cell having beneficial gene to make and use the invention without reasonable expectation of success.

The claims are broadly directed to the transplanting human stem cell rich population having the beneficial gene in methods of therapy, wherein stem cell are umbilical cord blood. The specification teaches cells expressing the desired beneficial gene and appropriate HLA genotype could be expanded ex vivo (in vitro) or in vivo. In a recent report, Grewal et al (Blood, 2003, 101 (11), 4233-4244) while reviewing the state of ex vivo culture UCB cells reported that the cytokine cocktails employed in the past studies included some but not all of the cytokines required to achieve UCB HSC expansion *in vitro*. In fact, Grewal assert that interpretation of using ex vivo culture of UCB is tempered by the knowledge that the conditions of culture used to date have not been shown to support USC amplification, only CFU

expansion (see page 362, col. 1, last para. bridging to col. 2, para. 1-2). The specification fails to provide conditions that would result in successful expansion of USC from cord blood. In addition, Grewal et al disclose that for UCBT, cell dose is the most critical determinant of outcome, and currently, 4 to 6 antigen HLA-matched grafts are considered acceptable. Grewal states "While the minimum acceptable UCB graft cell dose is yet to be unanimously agreed upon, a minimum threshold of 1.5 $x10^7$ nucleated cells/kg or 1.7 x 10^5 CD34 cells/kg has been suggested. In the instant case, specification fails to provide nexus between transplanting any dose of nucleated or CD34 positive cells to the treatment or reduction in HIV infection as embraced by the breadth of the claims. In addition, it is noted that independent claim 1 do not require identification of HLA genotype or phenotype of donor or recipient and thus embrace beneficial gene from an HLA unmatched genotype or phenotype. In a post filing report, Grewal et al while studying the role of UCB disclose that higher cell doses are even more important with HLA-mismatched grafts. Grewal emphasizes that although studies are awaited to delineate the relative importance of both HLA match and cell dose, however, they must be considered in the algorithm for UCB graft selection (see page 4240, col. 2, last para. bridging to 4241, col.1, para. 1), The specification fails to provide adequate guidance with respect to dose of UCB in HLA matched or unmatched genotype and phenotype. It is noted that at the time of filing of this application study has shown hat HLA class I B*5701 is highly associated with restriction of viral replication in nonprogressors (see, Flores-Villanueva et al. PNAS, 2001, 98:5140-5145), however, art also teaches that chronic infection with HIV-1 presents a formidable challenge to the *HLA*-restricted immune response from several perspectives. This includes the virus that infects and demolishes the very cells best equipped to dispatch that virus – CD4-bearing T cells. In addition, HIV-1 produces a genetic swarm of 10^9–10^{10} viruses per day, each with one or two new mutations, in an infected person. It is reasonable to conclude that depending upon

the duration of infection there would be ample opportunities for virus to mutate, evolve and adapt around the most sophisticated immune response. In addition, HIV-1 replicates in a diverse assemblage of cellular compartments from macrophages and lymphocytes to reproductive and neural tissue to intestinal and vaginal epithelia. These multiple cell reservoirs are effective factories for producing virus, and in certain cases sequestering virus from the immune system and from antiviral therapeutics (See O'Brien et al Trends Mol Med. 2001 Sep;7(9):379-81). It is noted that carriers of certain class I alleles (*HLA-B*27, -B*51* and *-B*57*) resulted in a delay in the onset of AIDS-defining diseases, whereas carriers of other alleles (*HLA-B*35, -Cw*04*) develop AIDS more rapidly. Furthermore, O'Brien et al and others also reported that HIV-1-infected individual that are homozygous for one or more class I (*A,B,* or *C*) loci progress to AIDS much more rapidly than individuals fully heterozygous at all three class I loci. In addition, O'Brien signals caution in interpreting the data of Flores-Villanueva due to several flaws in study design and emphasize more work is required to address this issue. In the instant case, the guidance provided in the specification is limited to a method of ensuring compatibility with the recipient HLA genotype. It is noted that claims embrace transplanting cells that have an unmatched or matched HLA genotype and phenotype. The specification fails to provide any guidance with respect to transplanting cells with alleles that delay the progression of infection particularly since prior art taught unpredictability with respect to role of HLA of different class and their association with HIV replication as evidenced by numerous alleles *HLA-B*35, -Cw*04* that develop AIDS more rapidly. The art of HLA playing a role in AIDS pathogenesis was evolving at the time of filing of this application. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art

how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*. In addtion, given that frequency of allele CCR5*59402A was increased in the HIV-positive cohort compared with healthy control (see Kaur et al, supra, table 3) suggesting this allele in fact might favor the likelihood of acquisition of HIV-1 infection. It would require undue experimentation for an Artisan to make and "use" the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled.

In some embodiments specification contemplates stem cell-rich cell populations are further enriched by tagging cell-surface markers of undifferentiated hematopoietic stem cells (HSC) (e.g., CD34, CD59, Thyl, CD38 low, C-kit low, lin-). However, prior to instant invention, HSCs are a broad class of cells that are a continuum of cells that have changing phenotypes. This is underscored by Coulombel (Oncogene, 2004, 23:7210-7222) who review the state of the art of identification of hematopoietic stem cells teach, "[t]he lack of specific markers and functional heterogeneity of even phenotypically pure populations of hematopoietic stem cells] explains why 20 years after their description ... indirect and retrospective functional assays remain essential to evaluate hematopoietic progenitor populations (see page 7210, col. 1-2, and bridging para)." Coulombel teach that assays must be established to distinguish the different stages along the developmental hematopoietic pathway (see figure 1 and pp. 7211-7212). The instant claims are not enabling for the breadth because, as evidenced by the art of record, HSCs encompass various cell types, each with a particular characteristic and differentiation potential. The specification identifies the cells differentiated from as HSCs, by use of marker such as samples can be enriched by tagging cell-surface markers of undifferentiated hematopoietic stem cells (e.g., CD34, CD59, Thyl, CD38 low, C-kit low, lin-) with fluorescently labeled monoclonal antibodies and sorting via fluorescence-activated cell sorting (FACS). However, as clearly

evidenced by the state of the art, a particular marker is not sufficient to uniquely identify a population of cells as HSCs cells, and further, that more characterization of the type of hematopoietic cell population is required to enable the claimed invention. Additionally, in a recent report Chao et al (Hematology, 2004, 354-371) conclude that "immune reconstitution after umbilical cord blood transplant is promoted by the increased generative capacity of UCBC HSC, and the decreased GVHD, but is hampered by fewer HSC, decreased adoptively transferred antigen-specific T cells, and functional defects in the T cells"(see page 369, col. 2, last para.). Additionally, several years after filing of this application Ballen (Blood, 2005, 105(10), 3786-3792) reported that "early infections continue to be a major problem in allogeneic cord blood transplantation. Ballen describes that because of the delayed immune reconstitution, infections are a serious problem in cord blood transplantations. Ballen cited multiple reports analyzing infections in several adult patients undergoing cord blood transplantation (also see Saavedra et al Bone Marrow Transplant. 2002;30: 937-943) including few deaths related to *Acinetobacter* infection. The specification does not provide any guidance with respect to overcome decreased adoptively transferred antigen-specific T cells, functional defects in the T cells or potential life threatening early infection in a human patient infected with HIV undergoing cord blood transplantation. An artisan would have to make new invention in the field to make and use the invention without reasonable expectation of success.

The Amount of Experimentation Necessary:

The claims are directed to broadly treating HIV infection in a patient by administration of stem cell rich population of cord blood having homozygous polymorphism in a CCR5 gene encoded CCR5 receptor via any route; however, the specification is not enabling for this breadth. For instance, given broadest reasonable interpretation an individual infected with chronic HIV could present entry of virus using multiple receptors in different race. The art clearly shows that

CCR5 is crucial in the infection stage of HIV. However, the working example is prophetic and do not compare the usage of alternative receptor nor discloses virus strain that exclusively uses CCR5 receptor for viral entry. Thus, it is unclear how, providing a specific cell type, with a particular allelic variant, would provide treatment, as CCR5 is found to be crucial in infection stages of HIV. The specification fails to correlate treating HIV infection, wherein HIV entry into an immune cell is facilitated by CCR5 receptor particularly since prior art taught multiple co receptor usage in HIV entry and alternate pathways of infection. The specification does not provide sufficient guidance to overcome this unpredictability for practicing the claimed method in-patient infected with HIV. The specification does not provide any guidance as to how would an artisan select which polymorphism would be beneficial for treating HIV infection caused by HIV in a given race particularly since art teaches that polymorphism such as *CCR5**59402A allele might favor the likelihood of acquisition of HIV-1 infection and development of AIDS (supra). Therefore, at the time of the invention there was no evidence of treating HIV infection caused by HIV in humans by transplanting cord blood cells with any beneficial gene having any polymorphism in a CCR5 gene having HLA matched or unmatched genotype and treatment of a HIV infection would have been predictable since a number of factors played role in the conferring resistance to HIV infection. As stated before that depending upon the duration of infection it is reasonable to state that virus would mutate, evolve and adapt around the most sophisticated immune response over a period of time (supra) particularly since HIV-1 replicates in a diverse cellular compartments from macrophages and lymphocytes to reproductive and neural tissue to intestinal and vaginal epithelia which would be effective factories for producing virus, and in certain cases sequestering virus from the immune system and from antiviral therapeutics (See O'Brien et al Trends Mol Med. 2001 Sep;7(9):379-81). Thus, skilled artisan would have to empirically practice the method in a reliable animal model to establish dose and effect of

nucleated or CD34+cell cord blood cells to overcome the problems of decreased adoptively transferred antigen-specific T cells, functional defects in the T cells or potential life threatening early infection in a human patient infected with HIV undergoing cord blood transplantation.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior arts do not teach a method of treating HIV infection in human by transplanting stem cell population having a beneficial gene that is polymorphism in CCR5 gene in humans. An artisan of skill would have required undue experimentation to practice the invention because the art of ex *vivo* cell therapy for the treatment of HIV in general was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant arguments filed on October 31, 2007 have been fully considered but they are not fully persuasive. Applicants, argue that Examiners improperly focused on inoperative embodiments and these embodiments are fully enabled. Applicants assert that the Office Action in large part alleges that undue experimentation is required to practice the invention. Applicants cite MPEP §2164.01, "the test of enablement is not whether any experimentation is necessary, but whether.., it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled

if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold,* 169 USPQ 299, 301 (C.C.P.A. 1971). Applicants further argue that, "[a] patent need not teach, and preferably omits, what is well known in art.

These arguments were fully considered but are not fully persuasive because the enablement rejection was not based on the inoperative embodiments rather on what has been taught in the specification for practicing the claimed invention and what is known in the art and whether an artisan of skill could make and use the claimed invention without undue experimentation. In response to applicants' discussion of *In re Cook and Merigold 169 USPQ 302*, it is noted that these case laws are not applicable in this case because, first, no embodiment is enabled in the instantly claimed invention and second, the enablement rejection was based on analysis according to In re Wands, as discussed in the MPEP. In contrast to applicants' arguments, Courts have stated, eg., "It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986).* However, that general, off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See *Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)*).

Applicants refer to declaration of Chow and Petz pertaining to rejections of expansion of cord blood cell consistent with the declaration that was withdrawn. Applicants assertion and the declaration is persuasive to the extent one of skilled in the art would be able to identify and collect cord blood cells having beneficial gene using the method described in instant application is persuasive.

Applicants argue that the claims have been amended to recite treatment of an HIV strain that enters an immune cell using a CCR5 receptor. Applicants also assert that the declaration with the previous response outlined the methods for transplantation of umbilical cord blood and replacement of the immune system in a human. Applicants assert that according to declaration, the particular disease treated by hematopoietic transplantation does not determine the dosage of stem cells used for treatment.

In response, it is noted that contrary to applicants' argument instant method does not preclude entry of HIV using other co receptor. Examiner has cited a number of references that clearly teaches HIV-1 entry into immune cells use other receptor in conjunction with CCR5 and claimed method does not preclude the entry of HIV by other receptor. Based on teaching in prior art it is reasonable to state that individual infected with chronic HIV could present entry of virus using multiple receptors in different race. The art clearly shows that CCR5 is crucial in the infection stage of HIV. However, the working example is prophetic and do not compare the usage of alternative receptor nor discloses virus strain that exclusively uses CCR5 receptor for viral entry. Thus, it is unclear how, providing a specific cell type, with a particular allelic variant, would provide treatment, as CCR5 is found to be crucial only in infection stages of HIV. The specification fails to correlate treating HIV infection, wherein HIV entry into an immune cell is facilitated by CCR5 receptor particularly since prior art taught multiple co receptor usage in HIV entry and alternate pathways of infection. The specification does not provide sufficient guidance to overcome this unpredictability for practicing the claimed

method in patient infected with HIV. The specification does not provide any guidance as to how an artisan would select polymorphism that would be beneficial for treating HIV infection caused by HIV in a given race particularly since art teaches that polymorphism such as CCR5*59402A allele might favor the likelihood of acquisition of HIV-1 infection and development of AIDS (supra). An artisan would have to perform undue experimentation to make and use of invention. With respect to applicant's argument of dosage of stem cell, it is noted that prior art of Grewal et al disclose that for UCBT, cell dose is the most critical determinant of outcome and instant specification fails to provide nexus between transplanting minimum threshold of nucleated cells or CD34+ cells to the beneficial outcome in the treatment of a complex immunodeficiency disease caused by HIV as embraced by the breadth of the claims. Applicant's declaration provides guidance with respect to a method that requires treatment of diseases using umbilical cord blood transplantation, including, *e.g.,* malignancies and benign genetic blood disorders. The declaration describes a patient is identified as a recipient of an umbilical cord blood transplant, the patient's own immune system is reduced or eliminated using, *e.g.,* radiation or chemotherapy. Umbilical cord blood is then administered to the patient to sufficient progeny in the patient to reconstitute an immune system for the patient. The method disclosed in the instant application is different from one claimed in the instant application that requires administration of cord blood to a HIV infected individual. It is generally known in the art that during HIV infection the lymph nodes and surrounding tissues become damaged; while HIV mutates and becomes more pathogenic leading to more T helper cell destruction. In the instant case, neither specification nor declaration provide enough evidence to support that transplanting cord blood as demonstrated for other disease would repopulate immune cells to keep up with replacing the T helper cells that are lost during HIV infection. It is apparent that one of skilled in the art would have to empirically test the claimed method in appropriate animal model to determine if enough of T cells

could be repopulated to effectively treat HIV infection over a period of time particularly since HIV infection is known to effect multiple organs including respiratory, gastro intestinal and central nervous system.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 17, 20, 24-25, 28-31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods for treating HIV infection by transplanting a stem cell rich population of cells (cord blood cells) obtained from a human donor having beneficial gene that is a homozygous polymorphism in any region of CCR5 gene thereby treating said HIV infection. In further embodiments, method comprising identification of the HLA genotype or phenotype of cells, screening cell sample from human donor to identify the stem cell rich population of the cell that has polymorphism in CCR5 gene by different techniques. Claims 28-31 further comprise identification of HLA genotype via high throughput such that genotype or phenotype of such cell is compatible with HLA genotype or phenotype of human..

In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features

and functional attributes that would distinguish different members of the claimed genus. The claims embrace polymorphism in any region or portion of CCR5 gene that provide resistance to HIV infection.

The specification teaches that the beneficial genes are beneficial for fighting HIV infection or render immune cells resistant to HIV infection, or genes that could be polymorphisms of genes encoding proteins expressed by immune cells. The specification also discloses gene can be a polymorphism to, CXCR4, CCR5, CCR2b, CCR3, and CCR1 including those that interfere with expression of the receptor at the cell surface (e.g., CCR5 delta 32, CCR5m303); ones that produce a receptor that is expressed, but unable to facilitate entry of the HIV virus (e.g., CCR2-64I); and promoter polymorphisms that regulate coreceptor expression (see pare 42 and 43 of the specification). The specification is silent, however, on any other polymorphism that could confer resistance to HIV infection. The specification additionally fails to disclose the nature of the association of genus of other polymorphism encoding the receptor or entry or infection with different strains of HIV that exclusively uses CCR5. The claims thus constitute a genus that encompasses plurality of polymorphism that confer resistance to HIV infection yet to be discovered, and since the specification only discloses limited species that may be capable of conferring resistance to infection, the disclosed structural features of said polymorphism do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not conclude that Applicant possessed any additional species, except for that of specifically described in specification (see para. 42 of the specification). Hence, only the polymorphism set forth in claims 15 and 16 could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that

Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:
[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus for contemplated biological activity.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims reads on transplanting stem cells having any beneficial gene that is a homozygous polymorphism in any CCR5 gene yet to be discovered for contemplated biological activity to confer resistance to HIV infection. The specification has exemplified use of the CCR5 delta 32, CCR5m303 (see under section of beneficial gene of this invention in the specification). However, specification fails to provide any specific guidance or structure of any other homozygous polymorphism in a CCR5 that confers resistance to HIV infection. For Recently, Kaur et al (Human Immunology 68, 454-461, 2007 and references therein) disclose percent allele frequencies corresponding to five SNPs in the promoter region of CCR5 at positions 59029, 59353, 59356, 59402, and 59653 in the HIV- 1 infected individuals. It is noted that

frequency of allele CCR5*59402A was increased in the HIV-positive cohort compared with healthy control (see table 3) indicating that *CCR5**59402A allele might favor the likelihood of acquisition of HIV-1 infection and development of AIDS (see Kaur et al page 459, col. 1, para. 1). It is generally known in prior art that polymorphisms influence HIV-1 transmission and disease progression differentially according to their distribution in a race-specific manner. The claimed invention as a whole is not adequately described since claims read on genus of homozygous polymorphism in CCR5 and specification fails to describe any other polymorphism in CCR5 other then those stated in specification (see para. 42 of the specification) that could confer resistance to HIV infection and which is not conventional in the art as of applicants effective filing date. In view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the cells having genus of homozygous polymorphism in any CCR5 gene. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

The skilled artisan cannot envision the detailed chemical structure of the encompassed homozygous polymorphism in CCR5 other then those desribed in the specification, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*,

25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of transplanting into the human cord blood having a gene that is a homozygous polymorphism in any region of CCR5 showing contemplated biological activity (capable of conferring resistance to the infection) at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Maintained-Double Patenting

Claims 1, 15-17, 20, 24-25, 27-31 and 33-34 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-17, 21-26, 36 and 40 of copending Application No. 10/498450 (US Patent Publication no 20050220772). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a method of treating HIV infection by transplanting stem cells having a beneficial gene. For example, claim 1 of instant application encompasses a method for treating HIV infection caused by M-tropic virus in humans by transplanting stem cell rich population of cell that has beneficial gene that is polymorphism in CCR5 gene. Claims 15-17 depend on method of claim 1 wherein polymorphism is either a 32-basepair deletions in coding region or CCR5m303 or in promoter region. Claim 18 depends on method of claim 1 wherein stem cell population will be selected from bone marrow, peripheral blood, umbilical cord blood and adipose tissue. Remaining claims are directed to screen cell sample from human donor to identify stem cell population having beneficial gene and

identification of HLA genotype or phenotype. Whereas, Claim 1 of the application No. 10/498450 is directed to a method of treating HIV infection in humans by screening plurality of cells to identify stem cells having beneficial gene and then transplanting stem cell with beneficial gene into HIV infected patients. The remaining claims encompass all the limitations of instant application. Thus, the claims of application no 10/498450 (US Patent publication no 20050220772) differ only with respect to broader scope of beneficial genes that could be used in the method for treating HIV infection, which encompasses polymorphism in CCR5 specifically claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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